

USSN 10/081,904

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Response Dated 14 March 2005

Reply to Office Action dated 15 November 2004

Remarks

Applicants have amended claims 1-8, 23, 25-27 and 29 to place the application in condition for allowance. Claims 24, 28 and 30-36 have been canceled without prejudice to renewal, but Applicants reserve the right to pursue these claims in divisional applications. Applicants very respectfully request rejoinder of process claim 26 and dependent claim 29 if claim 1 is found to be allowable.

Applicants thank the Examiner for providing "prior art made of record but not relied upon" in the office action and for suggestions and comments on proposed claim amendments. Applicants also thank the Examiner for filing the formal description of the interview on 3/2/05 stating that "the proposed claim amendments appear to address the 35 USC§112 rejections and overcome the art of record".

Support for the amendment of claim 1, insertion of semi-linear pathway representation (SLIPR), is found in the specification on page 17, the first paragraph of Example I; components, on page 1, first line of background, on page 7 in the definition for node and on page 11, three lines from the bottom of the page; and relational database, on page 9, in the first paragraph beginning on that page.

Support for the amendment of claim 2, use of the word components, is the same as for claim 1.

Support for the amendment of claim 3, use of standard methods, is found in the specification by definition in the middle of page 8; use of the phrase, optimize using linear next-neighbor criteria or global minimization criteria, in claim 34; and use of a method for constrained clustering, in claim 32.

Support for the amendment of claim 5 is found in the specification in the definition for pathway on page 7 which recites, "each pathway must contain at least two nodes and at least one mode".

Support for the amendment of claim 6, insertion of the list, gene expression studies including clone counting of cDNAs, ESTs, promoter regions, or regulatory sequences; electronic northern analysis; immunoprecipitation, microarray data, quantitative real-time polymerase chain reaction, transcript images; and yeast two hybrid data; a promoter similarity matrix, a protein-protein association matrix and a similarities among protein interactions matrix (SCIM matrix), is found in the specification in the first paragraph beneath the queries table on page 11 which recites, "protein-protein association matrix is based on gene expression studies including transcript images, clone counting of cDNAs, ESTs, promoter regions, or regulatory sequences expressed in or associated with a particular tissue or from microarray data, immunoprecipitation, from yeast two hybrid data, from quantitative real-time PCR (QPCR), and the like", and in claims 24 and 31.

Support for the amendment of claim 7, use of pairs or pairwise comparison, is found in the specification on page 19, second paragraph; on page 20, line 2; on page 28, in the second line of text and on page 29, in the first line of the second paragraph.

Support for the amendment of claim 8, insertion of the term nodes, is found in the specification on page 24, line 1.

Support for the amendment of claim 23 is found in the Summary of the specification beginning with

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the last paragraph on page 5 and ending with the next to the last paragraph of the Summary on page 6 and in the section of the specification entitled, Constrained Clustering Method, which begins near the bottom of page 28 and ends at the beginning of Example V on page 29..

Support for the amendment of claim 25, node-and-mode comparison predicts new homologous or orthologous pathways, is found in the specification on page 11, in the third paragraph (beneath the queries table) subheading entitled, "Node-and-mode comparisons" and in claim 28.

Support for the amendment of claim 26 is found in the original and amended claims, especially claim 28, as well as in the specification on page 23, Example IV, entitled PM_predict; on page 24, in the section entitled optimization algorithm; on page 28, in the section entitled, "Constrained clustering method", where the first sentence recites, "An alternative method for predicting novel pathways homologous to a known pathway uses constrained clustering"; and on page 14, third paragraph, in the description of Fig. 9, the end of which recites, "Homologous or orthologous pathways are reported...when the node and mode scores are sufficient to calculate an OS-score...".

Support for the amendment of claim 27 is the claim itself.

Support for the amendment of claim 28 is found on page 14, third paragraph, in the description of Fig. 9 as shown directly above at the end of support for claim 26.

Support for the amendment of claim 29 is the claim itself.

Claim Rejections - 35 USC § 112

The Examiner has rejected claims 1-8 and 23-36 under 35 USC§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that the word "means" is preceded by the words "data storage" in an attempt to use a "means" clause to recite a claim element as a means for performing a specified function. However, no function is specified; so it is impossible to determine the equivalents of the element, as required by 35 USC§112, sixth paragraph. The limitations following the recitation "data storage means" do not further limit the storage means.

Applicants have amended claim 1 to recite, "A computerized storage and retrieval system of biological information comprising: a means for entering data; a means for displaying the data; a programmable central processing unit for performing automated analysis using semi-linear pathway representation (SLIPR) and methods to compare and predict pathways and their components and to establish a pathways database; a means for storing the data; and a relational database containing annotated and curated pathways and information on the pathways and their components". The amendment presents parallel structure for each means; provides function (ie. "a means for storing data"); and sets forth the relational database as an element

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of the claimed system.

The Examiner states that claim 2 does not further limit the apparatus or system of claim 1, as the limitations regarding the type of data do not further limit the "storage means" itself.

Applicants have amended claim 2 to recite, "The system of claim 1, wherein the information pertaining to the pathways and their components and stored in a plurality of tables further comprises proteins, their sequences and attributes; protein interactions; protein-protein associations; protein pathways; mRNA, microarray, and protein expression data; genes, their sequences and attributes; descriptions of cells, tissues, and organs; pathology reports; and patient histories and treatments". Applicants respectfully submit the amendment now establishes the various types of curated and annotated information can be used to predict pathways and their components and establish a pathways database.

The Examiner states that claims 3 and 4 are unclear and asks: 1) if the list of functions is a pseudocode of all functions that must be performed and in that order, 2) if one or more of the functions can be performed in a different order, or 3) if the list represents capabilities or indicates specific programs?

Applicants have amended claim 3 to recite, "The system of claim 1, wherein the central processing unit is programmed to run an algorithm or a method for constrained clustering or an optimization algorithm for dynamic programming and one or more functions or standard methods selected from retrieve, input, edit, annotate, search, calculate similarities, align, compare, optimize using linear next-neighbor criteria or global minimization criteria, and predict homologous or orthologous pathways and their components and wherein the method for constrained clustering is further selected from average linkage, single linkage, complete linkage, K-means, or self-organizing maps".

Applicants have amended claim 4 to recite, "The system of claim 1, wherein the central processing unit is further programmed to perform one or more analyses selected from protein sequence analysis, protein interactions analysis, protein-protein association analysis, protein pathway analysis, gene expression analysis, pathway annotation analysis, pathway edit analysis, pathway expression analysis, tissue expression analysis, subtractive hybridization analysis, electronic northern analysis, and commonality analysis". With the amendment of claims 3 and 4, Applicants have clarified the use of the central processing unit (CPU) to run various algorithms, methods and analyses that compare and predict pathways and their components and establish a pathways database.

The Examiner states that claim 5 is confusing as the data should be entered into the system using the data entry means. It appears Applicant is attempting to limit the type or form of data to be entered, but that is not what the limitation recites.

Applicants have amended claim 5 to recite, "The system of claim 1, wherein each pathway in the database further comprises at least two nodes connected by a mode". With this amendment, Applicants have

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defined pathway as it is used in the patent and shown in Figure 1.

The Examiner states that claim 6 is a process limitation and not a further structural limitation of the system. It is essentially an intended use for the display means. It provides no structural limitation as to what the display means comprises.

Applicants have amended claim 6 to recite, "The system of claim 5, wherein at least two pathways are compared using scores calculated from sequence identity, motif or structural homologies that interrelate nodes and employing coefficients of similarity calculated or selected from gene expression studies including clone counting of cDNAs, ESTs, promoter regions, or regulatory sequences; electronic northern analysis, immunoprecipitation, microarray data, quantitative real-time polymerase chain reaction, transcript images; and yeast two hybrid data; a promoter similarity matrix, a protein-protein association matrix and a similarities among protein interactions matrix (SCIM matrix) that interrelate nodes of the pathways". With this amendment, Applicants have avoided process language and clarified the process for using scores and coefficients of similarity, respectively, to compare nodes and modes of pathways.

The Examiner has stated that in claim 7, it is unclear if the list of functions is a pseudocode of all functions that must be performed and in that order? Or can one or more functions be performed in differing order? Are these merely capabilities, or an indication of a specific program?

Applicants have amended claim 7 to recite, "The system of claim 1, wherein the central processing unit is programmed to perform pairwise comparison of at least two pathways or their components selected from node-only, mode-only, and node-and-mode comparison and wherein the node-only comparison is further selected from protein only, non-protein only, and protein and non-protein nodes". With this amendment, Applicants respectfully submit that they have clarified the pairwise comparison of nodes and/or modes as used in the invention.

The Examiner states that it is unclear, in claim 8, what data is used to run the dynamic programming algorithm. What data from the data storage means is to be utilized? Further in claim 8, the alignment of the "where $D > O$ " is not clear- is it intended to go before equation 2 ($w(a_{ik}, a_{ji}) = \dots$) or in the middle of it? It is unclear how step (c) is related to the results of step (b), and the term "using traceback" is not a positive active method step clearly identifying the step to be performed or data manipulation to be made.

Applicants have amended claim 8, as shown in above, to state that the algorithm works on "nodes", to show the correct placement of "where $D > O$ ", and to replace the jargon, "using traceback to identify putative pathways" with the phrase, "finding the best alignment to predict nodes of putative pathways...".

The Examiner states that in claim 23, the term "pair of proteins in the database" lack antecedent basis. The data storage means in claim 1 comprises protein pathways, (and annotated information about the

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pathway) and not the proteins themselves.

Applicants have amended claim 23, as shown above, to correct antecedent basis and to remove reference to the data storage means.

The Examiner states that claim 24 does not further limit the system/apparatus of claim 3. Applicants have canceled claim 24.

The Examiner states that claim 25 does not further limit the system/apparatus of claim 7. The limitations of claim 25 are process limitations which do not limit the structure of the system being claimed. It is unclear if Applicant intends these limitations to further limit a program or the central processing unit. The claim is not presently limited to that interpretation. In claim 25, the abbreviation SCIM should be spelled out at its first instance in the claims for clarity.

Applicants have amended claim 25 to recite, "The system of claim 7, wherein node-and-mode comparison predicts new homologous or orthologous pathways by comparing nodes using an optimization algorithm for dynamic programming or a constrained clustering algorithm and standard methods and modes by generating a SCIM matrix containing coefficients of similarity". Applicants respectfully submit that the claim now describes a preferred node-and-mode comparison; SCIM is now spelled out in claim 6.

The Examiner states that in claim 26, the limitations regarding protein sequences in the database lack antecedent basis in claim 1. The data storage means of claim 1 comprises protein pathways, (and annotated information about the pathways) and not the proteins themselves. Further in claim 26, the abbreviations OS-score should be spelled out at their first instance for clarity.

Applicants have amended claim 26 to recite, "A process for analyzing and predicting novel homologous or orthologous pathways comprising: a) submitting a query pathway and protein sequences; b) organizing the pathway and sequences using SLIPR; c) comparing each sequence of the query pathway with each sequence in the pathways database using an algorithm for constrained clustering or an optimization algorithm for dynamic programming and standard methods of protein comparison to calculate sequence identity score; d) using a SCIM matrix derived from protein interactions or protein-protein association analysis to compare coefficients of similarity for each interaction of the query pathway and each interaction for a pathway in the pathways database; e) calculating an overall-similarity score (OS-score) based on sequence identity scores and coefficients of similarity for each pathway; and f) retrieving pathways meeting a user-specified threshold for OS-score, thereby analyzing or predicting novel homologous or orthologous pathways". With this amendment, Applicants submit that they have corrected antecedent basis, clarified the steps of the process, and spelled out OS-score.

The Examiner states that claims 27-29, 33, and 34 do not further limit the system/apparatus of claim 3. The limitations of claim 27-29 are process limitations which do not limit the structure of the system being

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claimed.

Applicants have amended claim 27 to recite, "The system of claim 4, wherein protein interactions analysis between a query pathway and each pathway in the pathways database produces a coefficient of similarity to interrelate each mode of the query pathway and a mode of the most closely related protein pathway". As amended, claim 27 summarizes protein interactions analysis rather than presenting the steps of the process.

Applicants have canceled claim 28.

Applicants have amended claim 29 to recite, "The process of claim 26, wherein the predicted orthologous pathway further comprises orthologous proteins with the highest sequence identity to the proteins in the query pathway and protein interactions inherited from the query pathway". As amended, claim 29 defines one of the ways prediction of orthologous and homologous pathways can differ.

The Examiner states (in some detail) that claims 30-36 do not further limit the system/apparatus of claim 7. Applicants have canceled claims 30-36.

With the cancelation of claims 24, 28 and 30-36 and the amendments to claims 1-8, 23, 25-27 and 29, Applicants submit that they have overcome the rejection of claims 1-8 and 23-36 under 35 USC§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, and under 35 USC§112, sixth paragraph, no function specified.

Claim Rejections - 35 USC § 102

The Examiner has rejected claims 1-7, 24, 27-34 under 35 USC§102 (b) as being anticipated by Kuffner et al (Bioinformatics (2000) Ref. 13, PTO-1449). The Examiner states that the rejected claims are drawn to systems which comprise a data entry means, a display means, a CPU programmed to certain functions, and a data storage means, PETRI net, comprising biological pathway information and annotations in tables in a relational database. Kuffner discloses the use of differential metabolic display to compare specific systems—organisms, tissues or disease states with the biochemical knowledge contained in currently available, standard databases. The CPU can compare sequences and the presence of proteins in systems, develop pathways and connections between data in the database, etc. As such, Kuffner meets the limitations of the rejected claims.

Applicants respectfully submit that the use of semi-linear pathway representation, SLIPR, to compare nodes and modes and predict pathways and their components distinguishes the present invention from that of Kuffner. With the cancelation of claims 24, 28 and 30-36 and the amendments to claims 1-8, 23, 25-27 and 29, the claimed invention is no longer anticipated by Kuffner.

The Examiner has rejected claims 1-7, 24, 27-34 under 35 USC§102 (b) as being anticipated by Nakao et al (1999, Ref 6, PTO-1449). The KEGG system of Nakao et al comprises a data entry means (information about the array experiment and about each spot, p.2) a means for display (Figure 1, Java applets) a

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programmed CPU (sections 2.3, 2.4, 3.2, 3.3). The data storage means (the EXPRESSION database) comprise related tables of information regarding proteins and their interactions. This is a relational database meeting the limitations of claims 1-2. The information contemplated by Nakao et al to be used in their methods include gene and protein sequence information, annotations, Microarray data, expression data, data relating to diseases, etc. The CPU can compare sequences, compare presence of proteins in systems, develop pathways and connections between data in the database, etc. (Sections 2.3, 2.4, 3.2, 3.3, discussion). A standard representation for known metabolic pathways is used, KEGG or KEGG/LENZYME entry. As such, Nakao meets the limitations of the rejected claims.

Applicants respectfully submit that the use of semi-linear pathway representation, SLIPR, to compare nodes and modes and predict pathways and their components distinguishes the present invention from the system of Nakao. With the cancelation of claims 24, 28 and 30-36 and the amendments to claims 1-8, 23, 25-27 and 29, the claimed invention is no longer anticipated by Nakao.

The Examiner has rejected claims 1, 2, 4, and 5 under 35 USC§102 (b) as being anticipated by Seilhamer et al (USPN 6,023,659). Seilhamer discloses systems which comprise a data entry means, a means for displaying data, and programmable CPU, and a data storage means comprising annotated information about protein pathways (See Fig 2, 4A). The database system of Seilhamer is a relational database system of related tables. (col 2). The tables comprise information about proteins, their sequences, interactions, functions etc. The system can display lists of the tables (col 3) as well as a variety of other information (See figures). The programmed CPU can provide protein sequence analysis and comparisons, and predict functions based on sequence similarity scores. As such, Seilhamer anticipates the rejected claims.

Applicants respectfully submit that the use of semi-linear pathway representation, SLIPR, to compare nodes and modes and predict pathways and their components distinguishes the present invention from that of Seilhamer. With the amendment claims 1, 2, 4 and 5 as shown above, the claimed invention is no longer anticipated by Seilhamer.

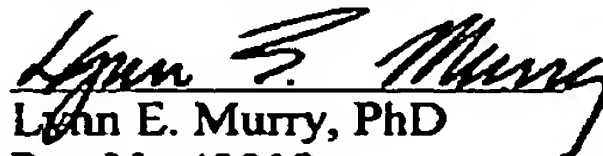
In that Kuffner, Nakao and Seilhamer do not anticipate the claimed invention, Applicants respectfully request that the rejection of claims 1-7, 24, 27-34 under 35 USC§102 (b) be withdrawn.

Conclusion

Applicants respectfully request that a timely Notice of Allowance be issued in this case. If Applicant's representative can aid the Examiner in this process, please call 479.973.0734.

Date: 14 March 2005
424 West Patricia Lane
Fayetteville AR 72703
Phone/Fax: (479) 973-0734

Respectfully submitted,


Lynn E. Murry, PhD
Reg No 42918